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REVIEW ARTICLE

The use of platelet-rich products for skin graft donor site healing: a systematic review and meta-analysis

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ABSTRACT

Split thickness skin grafting is a common reconstructive technique which carries unavoidable donor site morbidity. The aim of this systematic review and meta-analysis is to present the evidence for the use of platelet rich plasma as an adjunct to donor site wound healing. A comprehensive literature search was performed, according to PRISMA guidelines from inception to August 2020, for studies regarding platelet rich plasma and skin graft donor site healing. Animal studies, case series of less than three cases and studies reporting histological outcomes only were excluded. The literature search identified 114 articles. After applying the exclusion criteria, four randomised control trials and two case-control studies remained, incorporating a total of 218 wounds in 139 patients. Four out of six studies reported total healing times for donor site wounds. Pooled analysis showed a significant reduction in healing time when donor wounds were treated with PRP versus controls [MD 5.95, 95% CI 5.04–6.85, $p < 0.001$]. Of the five studies which reported pain at dressing change, four showed significantly reduced pain scores for the platelet rich plasma treated wounds versus control. There were no significant complications recorded in the treated wounds. The current evidence basis for platelet rich plasma in donor site healing is limited by heterogeneous methodology and reporting outcomes and low powered studies. Nevertheless, the preponderance of data supports its use for accelerating wound healing and reducing pain at dressing change. These preliminary findings need to be substantiated with higher powered randomised controlled trials with standardised PRP manufacture and reporting structures.

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KEYWORDS
Platelet-rich plasma; skin graft; donor site; wound healing; meta-analysis

Introduction

Split-thickness skin grafting (SSG) is a commonly used technique for skin defect reconstruction. An inherent drawback of the procedure is the formation of a secondary wound site and the associated morbidities including pain and scarring. Infection can further complicate donor site healing and delay patient recovery in up to 24% of cases [1]. It is therefore important to optimise wound healing conditions in order to minimise discomfort and re-epithelialisation times.

Platelet-rich plasma (PRP) is an autologous mixture of concentrated platelets and growth factors derived from centrifuged blood [2]. It is purported to accelerate soft tissue wound healing [3] and axonal regeneration [4,5], thereby reducing the morbidity associated with acute and chronic wounds [6–10]. These effects are attributed to the release of cytokines and growth factors from activated platelets including platelet derived growth factor (PDGF), endothelial growth factor (EGF), vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and platelet derived growth factor (PDGF) [11]. These anabolic substances stimulate cellular proliferation and epithelial cell migration at the wound site [12], and modulate the inflammatory to reduce prolonged inflammation [13].

There are numerous reports which conclude that PRP is a highly efficacious adjunct for acute [14–16] and chronic [17–20] wound healing. Despite these claims, it has been noted that there is a paucity of high quality studies comparing PRP to standard wound healing. A Cochrane review by Martinez-Zapata et al. cited small sample sizes and poor methodological quality as barriers to forming evidence based conclusions regarding PRP for chronic wound healing [21]. Similarly, a systematic review by Picard et al. found significant methodological heterogeneity amongst reports assessing PRP as an adjunct in acute surgical wounds [8]. To our knowledge, there have been no systematic reviews assessing PRP as an adjunct to skin graft donor site healing; therefore, the aim of this systematic review and meta-analysis is to analyse the published relevant evidence.

Methods

This systematic review and meta-analysis was conducted according to PRIMSA guidelines (Figure 1), and was registered on the PROSPERO database (ID: CRD42020207965). Inclusion and exclusion criteria for studies are specified in Table 1.

Outcome measures

The primary outcome was the effect of PRP on skin graft donor site healing. Therefore, time to complete healing/re-epithelisation, wound healing rate, degree of epithelialisation and transepidermal water loss (TWL) were considered as primary outcomes.

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Supplemental data for this article can be accessed here.

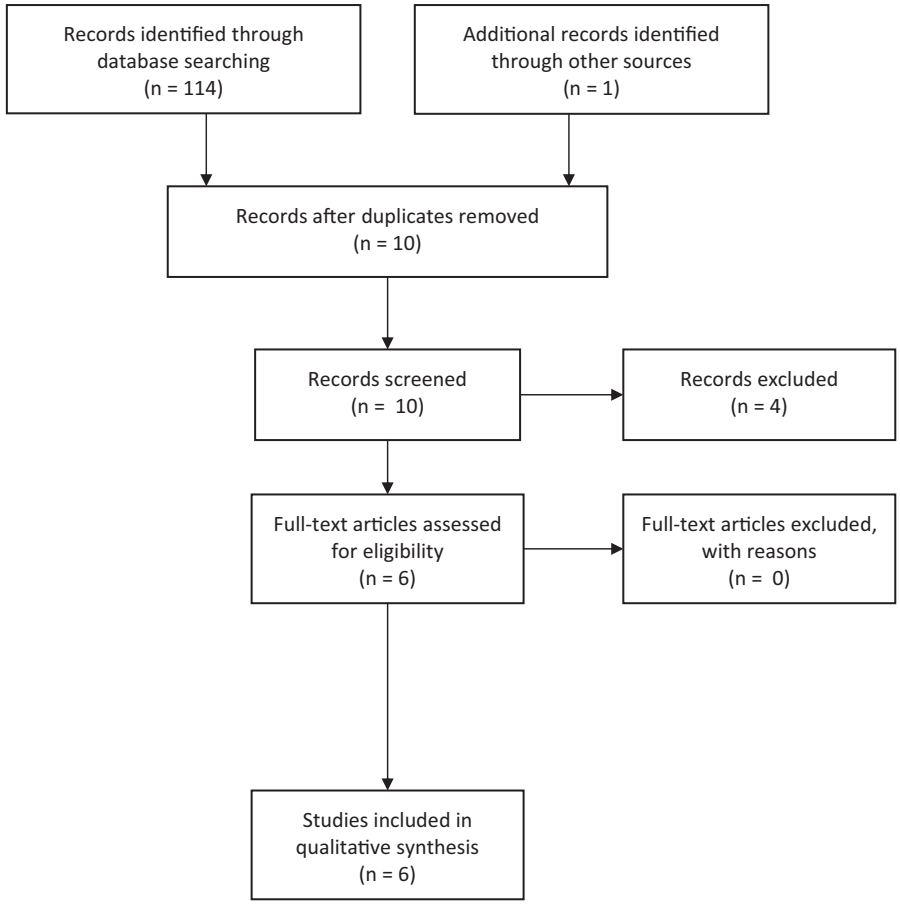

Figure 1. PRISMA flowchart.

Table 1. Patients, intervention, comparator, outcomes and study design criteria for inclusion and exclusion of studies.

Parameter	Inclusion criteria	Exclusion criteria
Patients	Adults (≥18)	Children
Intervention	Application of any PRP preparation to the skin graft donor site	PRP preparations with other biologically active agents added
Comparator	Any type of control donor site treated with dressings only	
Outcomes	Primary outcomes: Time to complete healing/ re-epithelisation, wound healing rate, degree of epithelialisation or transepidermal water loss Secondary outcomes: Pain score at dressing change, complications	Molecular or microscopic markers of wound healing
Study design	Randomised control trials, cohort studies, case-control studies and case series of greater than 3 cases	Expert opinion and preliminary reports, non-English articles and animal based studies

PRP: platelet-rich plasma.

Secondary outcomes included pain scores at dressing change and incidence of complications.

Search strategy

The MEDLINE, EMBASE and PubMed databases were searched for articles from inception to August 2020 using the terms: ('graft donor' AND 'PRP' OR 'platelet-rich plasma' OR 'platelet concentre(s)'). Duplicate results, animal studies and non-English studies were discarded. Additional articles were identified from review of the reference list of included studies.

Study selection

Two authors independently evaluated studies for relevance according to the inclusion/exclusion criteria.

Data extraction

Study data were extracted and independently verified by two authors. Bibliometric indices (authorship list, publication year, country in which study was conducted and type of study), population characteristics, skin graft dimensions, PRP formulation, wound dressings and clinical outcomes were recorded.

Results

A total of 114 studies were identified and six met the inclusion criteria (Figure 1). Of the six included studies, four were randomised control trials [22–25] and two were case-control studies [26,27]; these publications originated from Switzerland [23], Denmark [22], Iran [24], China [27], North America [26] and the Czech Republic [25] between 2008 and 2020 (Table 2). A total of 139 patients participated, and the mean age was 56 years.

Table 2. Overview of included studies.

Citation	Danielsen et al. [22]	Guerid et al. [23]	Miller et al. [26]	Fang et al. [27]	Slaninka et al. [25]	Vaheb et al. [24]
Year	2008	2013	2015	2019	2020	2020
Country	Denmark	Switzerland	USA	China	Czech Republic	Iran
Study type	RCT	RCT	Case-control	Case-control	RCT	RCT
GRADE rating	High	High	Moderate (inconsistency)	Low (significant bias & imprecision)	Low (significant bias & imprecision)	High
Number of patient						
PRP	20	15	5	15	21	33
Control		15		15		
Number of wounds						
PRP	20	15	5	15	21	33
Control	20	15	5	15	21	33
Mean age, years (SD)						
PRP	72.5 (median)	42.5 ± 3.1	48.4 ± 17.6	37 (8.1)	60 (M), 70 (F)	33.1 ± 2.6
Control		45.5 ± 3.9		35 (9.4)		
Wound site						
PRP	Thigh (20)	Thigh (15)	Thigh (5)	Back (10), thigh (3), pleurobranch (2)	Thigh (21)	Thigh (33)
Control	Thigh (20)	Thigh (15)	Thigh (5)	Back (11), thigh (3), pleurobranch (1)	Thigh (21)	Thigh (33)
Donor wound size, cm^2						
PRP	57.3 (22.5–84.5)	180 (25–200)	122 (8–500)	20–200	NR	188 ± 25.5
Control	62.5 (22.3–83.0)		140 (8–616)			190 ± 26.2
Graft thickness, mm	0.3	0.2	0.4–0.5	0.4–0.6	0.2	0.3–0.5
Autologous blood volume for PRP, ml	120	8.5	40–180	45	10	10
PRP processing	Centrifugation using the "Vivostat" system, followed by combination with "fibrin-I" solution and "pH 10 buffer". Half applied to donor site.	Centrifugation for 8 min at 2800 rpm.	Centifugation followed by mixture with thrombin and calcium chloride.	Two-step centrifugation. Platelet concentrate mixed with 10% calcium chloride to form PRP gel.	Centrifugation at 3600 rpm for 10 mins. Excess plasma mixed with platelets.	"Choukroun's protocol:" Centrifugation at 3000 rpm for 10 min.
Control	Dressings only	Dressings only	Dressings only	Dressings only	Dressings only	Dressings only
Interface dressing	Petrolatum fabric dressing, calcium alginate	Paraffin gauze	Control: Xeroform Intervention: orbaView (Centurion Medical)	Petrolatum gauze	Vaseline impregnated gauze and outer dry gauze	Vaseline gauze

NR: not recorded; PRP: platelet-rich plasma; RCT: randomised controlled trial; SD: standard deviation.

Risk of bias was estimated using the Cochrane Collaboration tool for risk of bias assessment for RCTs (Supplemental Table 1) [28], and Newcastle–Ottawa scale for non-RCTs (Supplemental Table 2) [29]. The GRADE approach was then applied by two independent researchers to determine the quality of evidence of each included study (Table 2) [30].

All teams harvested skin grafts from the thigh, with the exception of Fang et al. who included donor sites on the back [27]. There was substantial inter and intra-study variability regarding skin graft dimensions; this ranged from 8–616 cm^2 surface area and 0.2–0.6 mm depth, however all groups reported consistency amongst treatment arms.

Three studies compared healing outcomes for control and PRP treated donor sites created simultaneously in the same patient [22,24,25], whilst one compared outcomes in the same patients several years apart [26]. Two studies enrolled different patients in each treatment arm, either through randomisation [23] or retrospective selection [27]. Both studies reported similar average age and gender split across treatment groups, however other parameters including comorbidities were not compared.

There was heterogeneity amongst PRP collection and processing techniques. PRP was obtained from autologous blood *via* venepuncture in all studies, however the volume collected ranged from 8–180ml and there was no discussion of baseline platelet count. Five studies collected the same volume of blood in each patient [22–25,27], whilst one group obtained a range of volumes without clear justification [26]. A single or two-stage centrifugation process was then used at speeds of 2800–3600rpm for up to 10 min in order to isolate the 'buffy coat layer'. This was subsequently combined with fibrin solution and buffer [22], calcium chloride [26,27] or additional plasma [25] to form the final PRP mixture. Each group then applied the entire PRP solution to the donor site with the exception of Danielsen et al., who only applied half of the mixture (the remaining half used being used for the recipient wound) [22].

All six studies compared PRP treated donor sites to controls with dressing-only treatment (Table 2). A variety of interface dressings were used including petrolatum fabric [22,27], paraffin gauze [23], Vaseline impregnated gauze [24,25], which were consistent across treatment arms with the exception of the study by Miller et al., who used Xeroform and orbaView in the control and intervention groups respectively [26].

Slalinka et al. and Vaheb et al. reviewed the donor site wounds post-operatively at one day intervals starting from day 1 and day 8 respectively [24,25], whilst Guerid et al. performed alternate day reviews from post-operative day 5 [23]. Danielsen et al. and Miller et al. carried out donor wound assessments on day 5 and 8 [22], and day 7 respectively [26], whilst Fang et al. did not comment on the timeline for wound healing measurement [27].

Effect of intervention

Four studies reported results on donor site wound healing time (Table 3) [23–25,27]. Pooled analysis showed a significant reduction in healing time when donor wounds were treated with PRP versus controls [MD 5.98, 95% CI 5.09–6.87, $p < 0.001$] (Figure 2), with moderate asymmetry observed in the funnel plot (Figure 3). The mean number of days for total healing in the PRP and control groups were 7.2 ± 0.4 and 13.9 ± 1.0 respectively in the RCT by Guerid et al. [23], 11.8 ± 3.5 and 16.3 ± 4.3 respectively in the RCT by Vaheb et al. [24], 13.9 ± 4.7 and 17.7 ± 5.1 in the case control study by Fang et al. [27], and 14.9 ± 2.4 and 18.4 ± 2.9 in the RCT by Slaninka et al. [25].

Danielsen et al. recorded successive percentage epithelialisation and day 8 TWL, and found no significant differences between the PRP and control groups [22].

Meta-analysis for pain scores was precluded by the heterogeneous nature of the studies with respect to outcome measures (Table 3), therefore a narrative synthesis of results has been performed.

Pain scores were assessed using a variety of metrics including the visual analogue score (VAS), Likert and numerical scale (Table 3). Guerid et al. found a significant reduction in VAS scores on day 5 for the PRP group versus controls (mean 7.0 and 1.2 respectively) [23]. Similarly Fang et al. found a significant reduction in pain scores in the PRP group versus controls on day 7 (mean 3.1 ± 0.3 and 3.7 ± 0.2 respectively) day 10 (2.4 ± 0.1 and 3.4 ± 0.3 respectively) and day 14 (1.8 ± 0.2 and 2.7 ± 0.2 respectively) [27], as did Vaheb et al. on day 8 (mean 3.4 ± 0.4 and 5.6 ± 0.5 respectively) and day 15 (mean 2.8 ± 0.3 and 3.5 ± 0.4 respectively) [24]. Miller et al. assessed pain scores on day 7 using the Likert scale, and also found comparably favourable results for the PRP group compared to controls (mean 3.0 ± 3.7 and 7.2 ± 2.6 respectively) [26]. In contrast, the RCT conducted by Danielsen et al. found no statistically significant difference in pain scores on day five using a numerical rating system [22].

Three of the studies reported no adverse outcomes for either intervention [22, 23, 26], whereas one reported donor site infection in three of the control wounds (Table 3) [25]. Two studies did not report on incidence of adverse events [24,27].

Discussion

This systematic review and meta-analysis was performed with the aim of evaluating the efficacy of PRP for skin graft donor site healing. Data were collated from four RCT's [22–25] and two case-control studies [26,27], incorporating a total of 218 wounds on 139 patients. Despite some heterogeneity amongst study methodology and reporting outcomes, the overall evidence supports PRP for improving donor site healing time and pain.

The four studies which directly measured wound healing times consistently favoured PRP over dressing-only controls (Table 3) [23–25,27]. Average healing times for PRP and controls were significantly improved in all respective studies and in pooled analysis. Only one study found no significant difference in wound healing parameters compared to controls, which may be attributable to differences in PRP harvesting methods and earlier outcome measurements [22].

The precise mechanism behind accelerated donor wound healing with PRP is poorly understood. Histological analysis of PRP treated donor sites treated reveals a range of microscopic changes including enhanced fibroblast and keratinocyte proliferation, hypergranulosis, hyperkeratosis and angiogenesis [31,32]. The combined effect of these changes are thought to be faster epithelialisation and greater vessel formation [32]. However, the exact type and proportion of cytokines/growth factors which are needed to produce this effect remains to be determined. Multiple potential candidates exist including VEGF, an inhibitor of endothelial apoptosis and enhancer of vascular permeability, EGF, a potent stimulator of differentiation and migration of epithelial cells, PDGF, a mitotic promoter and stimulator of angiogenesis and bFGF, a mitogenic factor involved in wound healing. The current lack of standardised protocols for preparing PRP limit the usefulness of comparing different study outcomes and preclude formal mechanistic analysis [33].

Table 3. Outcomes of includes studies.

Citation	Danielsen et al. [22]	Guerid et al. [23]	Miller et al. [26]	Fang et al. [27]	Slaninka et al. [25]	Vaheb et al. [24]
Donor site review	Day 5 and 8	Day 5 and subsequent 2 day intervals	Day 7	NR	Day 1 and subsequent 1 day intervals	Day 8 and subsequent 1 day intervals
Pain score						
PRP	Numerical (0-10): 3.0 (day 5)	VAS: 7 (day 5)*	Likert: 3 ± 3.7 (day 7)*	VAS: 3.7 ± 0.2 (day 3) 3.1 ± 0.3 (day 7)* 2.4 ± 0.1 (day 10)* 1.8 ± 0.2 (day 14)* 1.2 ± 0.5 (day 21)	NR	VAS: 3.4 ± 0.4 (day 8)* 2.8 ± 0.3 (day 15)*
Control	Numerical (0-10): 4.0 (day 5)	VAS: 1.2 (day 5)*	Likert: 7.2 ± 2.6 (day 7)*	VAS 3.9 ± 0.16 (day 3) 3.7 ± 0.15 (day 7)* 3.4 ± 0.25 (day 10)* 2.7 ± 0.21 (day 14)* 1.5 ± 0.63 (day 21)		VAS: 5.6 ± 0.5 (day 8)* 3.5 ± 0.4 (day 15)*
Total healing time, days						
PRP	NR	7.2 ± 0.4*	NR	13.9 ± 4.7*	14.9 ± 2.4*	11.8 ± 3.5*
Control		13.9 ± 1.0*		17.7 ± 5.1*	18.4 ± 2.9*	16.3 ± 4.3*
Epithelialisation %						
PRP	44.5 ± 24.3 (day 5) 75.6 ± 25.1 (day 8)	NR	NR	NR	NR	NR
Control	48.6 ± 30.9 (day 5) 83.3 ± 23.0 (day 8)					
Transepidermal water loss, g/m^2/h (25–75% range)						
PRP	75.6 (65.6–84.9) (day 8)	NR	NR	NR	NR	NR
Control	71.9 (65.6–76.3) (day 8)					
Adverse outcomes	Nil	Nil	Nil	NR	3 wounds in control arm developed localised infection	NR

NR: not recorded; PRP: platelet-rich plasma; RCT: randomised controlled trial; SD: standard deviation; VAS: visual analogue score.
*Indicates statistically significant difference in favour of PRP treated wound vs control ($p < 0.05$).

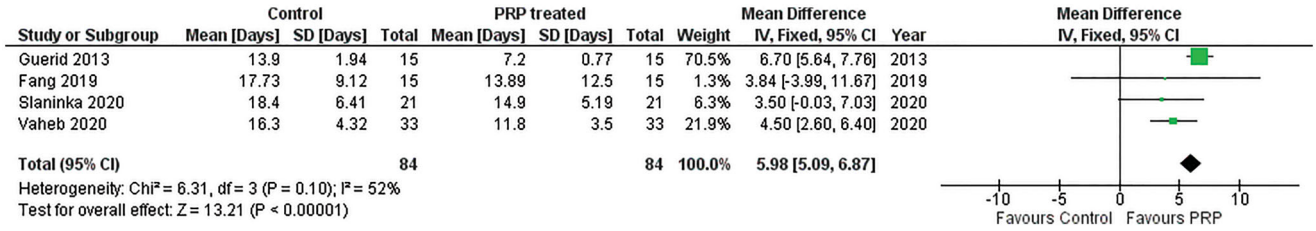

Figure 2. Forest plot showing significantly decreased healing time for donor sites treated with PRP versus controls.

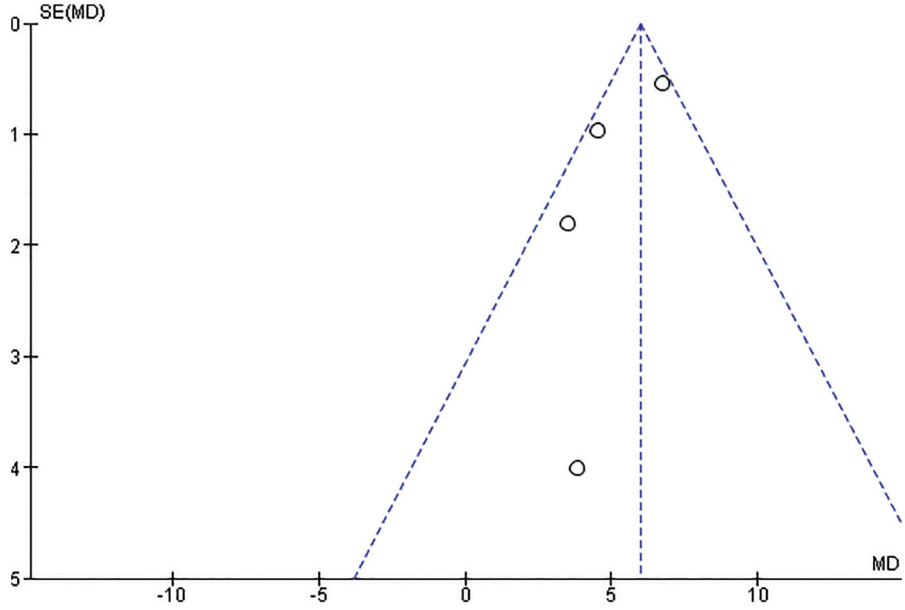

Figure 3. Funnel plot for bias assessment in donor site healing time.

Four out of the five studies which analysed pain scores reported statistically significant reduction in pain in the PRP group versus controls at dressing change (Table 3) [23,24,26,27]. Similar analgesic effects of PRP have been documented in other conditions including total shoulder arthroplasty [34], osteoarthritis [35,36], pilonidal disease [37], and chronic wounds [38]. This effect may be a direct consequence of analgesic factors released from activated platelets onto the donor wound bed including PDGF, VEGF and transforming growth factor beta-1 [39]. Alternatively, it may be a consequence of retained moisture at the donor site following application of the PRP gel/liquid mixture, which can facilitate dressing change [40]. Additional control groups with moist gel treatment over donor graft sites are needed to further investigate this effect.

There are a number of important limitations to discuss. Only four studies were included in the meta-analysis of donor wound healing times, one of which was an observational study, with clear heterogeneity in the methodologies. There was little consistency amongst PRP processing methods, and no rationalisation for the amount or concentration of PRP mixture applied to each wound. Moreover, there was substantial heterogeneity amongst dressing choices and interval between dressing changes, along with choice of control.

The meta-analysis showed moderate statistical heterogeneity ($I^2 = 52\%$), which may reflect these variances in methodology.

Other limitations included inconsistently reported outcomes for pain scores, which ultimately precluded formal meta-analysis of secondary outcomes.

Higher powered randomised controlled trials with standardised PRP manufacture and reporting structures are needed to rigorously compare wound healing outcomes.

Conclusion

The current evidence basis for platelet rich plasma in donor site healing is limited by heterogeneous methodology and reporting outcomes and low powered studies. At present, there is currently only a modest amount of evidence supporting the efficacy of PRP for donor site healing and pain reduction. These preliminary findings need to be substantiated with higher powered randomised controlled trials with standardised PRP manufacture and reporting structures.

Disclosure statement

The authors have no conflicts of interest to declare.

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